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(54) Title: METHODS FOR TREATING NEURODEGENERATIVE DISEASES AND DISORDERS USING N-(2,6-DISUBSTITUTED AROMATIC)-N'-PYRIDINYL UREAS AND OTHER ANTICONVULSANT COMPOUNDS

(57) Abstract

The instant invention is novel uses of known N-(2,6-disubstituted phenyl)-N'-3- and 4-pyridinyl ureas and pharmaceutically acceptable acid addition salts thereof. Such compounds as N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea monohydrochloride or N-(2,3-dichlorophenyl)-N'-4-pyridinyl urea are used for treating neurodegenerative disorders, perinatal asphyxia, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. The instant invention is similar novel uses of known anticonvulsant compounds as ralitoline, phenytoin, lamotrigine, tetrodotoxin, lidocaine, and carbamazepine.

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METHODS FOR TREATING NEURODEGENERATIVE
DISEASES AND DISORDERS USING
N-(2,6-DISUBSTITUTED AROMATIC)-N'-PYRIDINYL UREAS
AND OTHER ANTICONVULSANT COMPOUNDS

5

BACKGROUND OF THE INVENTION

The present invention relates to novel therapeutic
uses of a known compound, N-(2,6-disubstituted
10 aromatic)-N'-pyridinyl ureas, its derivatives, and
pharmaceutically acceptable salts. The present
invention also relates to novel therapeutic uses of
various other anticonvulsant drugs, their derivatives,
and pharmaceutically acceptable salts. The present
15 invention concerns a method for treating
neurodegenerative diseases and disorders in a mammal in
need of such treatment.

Such neurodegenerative diseases are, for example,
Alzheimer's disease, Huntington's disease, Parkinson's
20 disease, and Amyotrophic Lateral Sclerosis.

The present invention also covers treating
neurodegenerative disorders termed acute brain injury.
These include but are not limited to: stroke, head
trauma, and asphyxia.

25 Stroke refers to a cerebral vascular disease and
may also be referred to as a cerebral vascular
incidence (CVA) and includes acute thromboembolic
stroke. Stroke includes both focal and global
ischemia. Also included are transient cerebral
30 ischemic attacks and other cerebrovascular problems
accompanied by cerebral ischemia. A patient undergoing
carotid endarterectomy specifically or other
cerebrovascular or vascular surgical procedures in
general, or diagnostic vascular procedures including
35 cerebral angiography and the like.

Other incidents are head trauma, spinal cord
trauma, or injury from general anoxia, hypoxia,

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hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as those suffering from stroke for administration by methods of the present invention.

After ischemia of the brain in vivo many changes take place. There is a rapid loss of synaptic activity, a large shift in extracellular voltage, a release of the neurotransmitter glutamate, and a loss of ion homeostasis. The excess release of glutamate may be especially important in ischemic injury. Glutamate is an excitotoxin, meaning that overstimulation of glutamate receptor-linked channels allows excess calcium and sodium influx into neurons leading to neuronal death.

The overstimulation of receptors is thought to be involved in the etiology of several neurological disorders, i.e., epilepsy and cerebral ischemia. Evidence is also accumulating that the brain damage associated with anoxia, stroke, hypoglycemia, epilepsy, and perhaps neurodegenerative illnesses such as Alzheimer's or Huntington's diseases may be at least partially produced by excessive activation of N-methyl-D-aspartic acid (NMDA) receptors (Kemp JA, Foster AC, Wong EHF, _Trends in Neurosciences_, 1987;10(7):294-8).

The present invention employs the use of anticonvulsant compounds, such as the compounds of Formula I which are phenyl pyridinyl ureas as a method

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of blocking or delaying damage to neurons from
conditions similar to ischemia. It is believed that by
preventing neuronal damage, the compounds of Formula I,
alone or together with a pharmaceutically acceptable
5   carrier, can be used to treat neurological diseases
such as Alzheimer's disease, Huntington's disease,
Parkinson's disease, myotropic lateral sclerosis, and
disorders such as stroke, head trauma, and asphyxia.
The present invention is also directed to similar uses
10   and methods of treatment employing other anticonvulsant
compounds disclosed herein.

Various substituted phenyl pyridinyl ureas have
been described but none having neuroprotective
activity. For example, Bruce MI, Zwar JA, _Proc Roy Soc_
15   (London), _Sec. B. 165_ (999), 1966;245-65 disclose many
N-mono- and N,N'-disubstituted ureas having cytokinin
activity. N-(3,4-dichlorophenyl)-N'-3- and 4-pyridinyl
ureas show such activity whereas the corresponding
2,5-dichloro compounds were inactive. In general, the
20   authors concluded that phenyl ring substitution
enhanced activity with meta substituents providing
highest activity and ortho substituents lowest
activity.

German Patent Publication 2,928,485 also describes
25   various ureas including N-(3-chloro-4-trifluoromethyl-
phenyl)-N'-3- and 4-pyridinyl ureas as being useful for
inhibiting lipid absorption.

French Patent Publication 2,155,856 teaches
various 2-pyridinyl ureas including N-(3,4-
30   dichlorophenyl)-N'-2-pyridinyl urea as having
antiinflammatory and analgesic activity.

U.S. Patent Number 4,629,731 covers the phenyl
pyridinyl urea compounds of the instant invention,
methods for preparing them, and their use as an
35   anticonvulsant. The term convulsions is intended to
mean the characteristic body movements which are
associated with the group of chronic central nervous

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system disorders termed epilepsies. The patent is
hereby incorporated by reference.

   There is no disclosure in the above references
to suggest the present invention's novel uses of
5   compounds of U.S. Patent Number 4,629,731 to treat
neurodegenerative diseases and disorders in a mammal in
need of such treatment.

10   SUMMARY OF THE INVENTION

   The present invention relates to novel uses of
anticonvulsant compounds such as the known compounds of
the formula

15

I

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wherein A is 3- or 4-pyridinyl; R_1 and R_2 are each
independently halogen, lower alkyl, lower alkoxy, lower
alkanoyl, lower alkoxycarbonyl, or nitro, and R_3 is
25   hydrogen, halogen, lower alkyl, lower alkoxy, lower
alkanoyl, lower alkoxycarbonyl, or nitro, or a
pharmaceutically acceptable acid addition salt thereof.
   The present invention also relates to novel uses
of various other anticonvulsant compounds such as
30   ralitoline, phenytoin, lamotrigine, tetrodotoxin,
lidocaine, and carbamazepine.
   The present invention further includes novel uses
of a pharmaceutical composition comprising a
neuroprotective effective amount of a compound of
35   Formula I or other anticonvulsant compounds together
with a pharmaceutically acceptable carrier.

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The novel uses of the instant invention concerns a method for treating neurodegenerative diseases or disorders in mammals suffering therefrom by administering to such mammals a neuroprotective

5   effective amount of a compound of Formula I or the additionally disclosed anticonvulsants, or a compound of Formula I or the additionally disclosed anticonvulsants together with a pharmaceutically acceptable carrier, in unit dosage form.

10

Brief Description of the Drawings

Figure 1 are graphs reporting oxygen-tension measurements made with an oxygen-sensitive microelectrode in Example 3.

15   Figure 2 is a graph reporting that the percentage of slices that recovered at least half of their Prehypoxic-Hypoglycemic Synaptic Potential Amplitude increased with increasing concentrations of a compound of Formula I.

20   Figure 3 are graphs of the mean EPSP Amplitudes at the end of the experiments conducted in Example 3.

Figure 4 is a graph indicating that the percentage of slices that recovered at least half of their Prehypoxic-Hypoglycemic Synaptic Potential Amplitude

25   varied with drug treatments.

DETAILED DESCRIPTION OF THE EMBODIMENTS

30   The term "halogen" as used herein in the definition of the compounds of the Formula I includes fluorine, chlorine, bromine, and iodine.

The term "lower" in reference to alkyl, alkoxy, alkanoyl, and alkoxycarbonyl pertains to a straight or

35   branched carbon chain of from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, or t-butyl.

The compounds of structural Formula I are basic in nature and form pharmaceutically acceptable salts with both organic and inorganic acids. Examples of such acids are acetic, hydrochloric, phosphoric, nitric,

5 sulfuric, fumaric, citric, maleic, malic, and the like. The salts are prepared by contacting the free base form of the pyridinyl urea with an equivalent amount of the desired acid in the conventional manner. The free base forms may be regenerated by treating the salt form with

10 a base. For example, dilute aqueous basic solutions may be utilized. Dilute aqueous sodium hydroxide, sodium carbonate, or ammonia are suitable for this purpose. The free base forms differ from their respective salt forms somewhat in certain physical

15 properties such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

The compounds of the invention of Formula I can exist in unsolvated as well as solvated forms,

20 including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like are equivalent to the unsolvated forms for purposes of the invention.

A preferred embodiment of the compound of the

25 Formula I employed as a neuroprotective agent is where R_3 is hydrogen or a pharmaceutically acceptable acid addition salt thereof.

Another preferred embodiment of the compound of the Formula I is where R_1 and R_2 are each independently

30 halogen or lower alkyl, or a pharmaceutically acceptable acid addition salt thereof.

Still another preferred embodiment of the compound of Formula I is where R_1 and R_2 are each independently chlorine or methyl.

35 Particular embodiments are the following compounds:

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N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea
monohydrochloride;

N-(2,3-dichlorophenyl)-N'-4-pyridinyl urea;
N-(2,6-dichlorophenyl)-N'-4-pyridinyl urea;
N-(2,6-dichlorophenyl)-N'-3-pyridinyl urea;
N-(2,6-dimethylphenyl)-N'-4-pyridinyl urea;
N-(2,6-dimethylphenyl)-N'-3-pyridinyl urea;
N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea;
N-(2-chloro-6-methylphenyl)-N'-3-pyridinyl urea;
N-(2,6-diethylphenyl)-N'-4-pyridinyl urea;
N-(2,6-diethylphenyl)-N'-3-pyridinyl urea;
N-(2,6-dimethyl-4-bromophenyl)-N'-4-pyridinyl
urea;
N-(2,6-dimethyl-4-bromophenyl)-N'-3-pyridinyl
urea;
N-(2,4,6-trimethylphenyl)-N'-4-pyridinyl urea;
N-(2,4,6-trimethylphenyl)-N'-3-pyridinyl urea;
N-(2,4,6-trichlorophenyl)-N'-4-pyridinyl urea;
N-(2,4,6-trichlorophenyl)-N'-3-pyridinyl urea;
or a pharmaceutically acceptable acid addition
salt thereof.

The compounds of Formula I may be prepared by
reacting an isocyanate of the formula

II

with an equimolar amount of 3- or 4-aminopyridine in an
inert solvent, such as tetrahydrofuran, dioxane, and
the like, at elevated temperatures, such as at the
boiling point of the solvent used.

The starting materials such as the various
isocyanates are known and can be purchased commercially
or synthesized by known methods.

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The additional compounds, which are anticonvulsant compounds and can be used as agents for treating neurogenerative diseases or disorders as heretofore discussed, include ralitoline, phenytoin, lamotrigine,

5 tetrodotoxin, lidocaine, and carbamazepine. The methods for making and administering each of these compounds are known to those skilled in the art and can be shown respectively by reference to the following publications: European Patent 124,911, U.S. Patents

10 2,409,754 and 4,602,017, Kishi et al, Am Chem Soc 1972;94:9219, U.S. Patents 2,441,498 and 2,948,718. As it will be illustrated at a later point, each of these compounds have been shown in vitro to have neuroprotective capabilities.

15 It should be understood that the present invention is not limited to the use of the anticonvulsant compounds disclosed herein. Similar compounds which prevent irreversible neuronal damage from conditions similar to ischemia are also included in the present

20 invention. In addition, anticonvulsant compounds that bind to sodium channels or that cause a voltage-dependent block to sodium currents or that modulate ion channels without simply blocking them are also included in the present invention.

25 The compounds of structural Formula I, and the additionally disclosed anticonvulsant compounds, can be prepared and administered in a wide variety of oral and parenteral dosage forms. The compounds of structural Formula I or the other disclosed anticonvulsant

30 compounds can also be administered intravenously. For example, a useful oral dosage is between 50 and 5000 mg, a useful parenteral dosage is between 50 and 2000 mg, and a useful intravenous dosage is between 10 and 1000 mg.

35 For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either

solid or liquid. Solid form preparations include
powders, tablets, dispersible granules, capsules,
cachets, and suppositories. A solid carrier can be one
or more substances which may also act as diluents,
flavoring agents, solubilizers, lubricants, suspending
agents, binders, or tablet disintegrating agents; it
can also be an encapsulating material. In powders, the
carrier is a finely divided solid which is in admixture
with the finely divided active compounds of the present
invention. In the tablet the active compound is mixed
with carrier having the necessary binding properties in
suitable proportions and compacted in the shape and
size desired. The powders and tablets preferably
contain from 5% to 10% to about 70% of the active
ingredient. Suitable solid carriers are magnesium
carbonate, magnesium stearate, talc, sugar, lactose,
pectin, dextrin, starch, gelatin, tragacanth, methyl
cellulose, sodium carboxymethyl cellulose, a low
melting wax, cocoa butter, and the like. The term
"preparation" is intended to include the formulation of
the active compound with encapsulating material as
carrier providing a capsule in which the active
component (with or without other carriers) is
surrounded by carrier, which is thus in association
with it. Similarly, cachets are included. Tablets,
powders, cachets, and capsules can be used as solid
dosage forms suitable for oral administration.

Liquid form preparations include solutions,
suspensions, and emulsions. As an example, water or
water-propylene glycol solutions may be mentioned for
parenteral injections. Liquid preparations can also be
formulated in solution in aqueous polyethylene glycol
solution. Aqueous solutions suitable for oral use can
be prepared by dissolving the active component in water
and adding suitable colorants, flavors, stabilizing,
and thickening agents as desired. Aqueous suspensions
suitable for oral use can be made by dispersing the

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finely divided active component in water with viscous
material, i.e., natural or synthetic gums, resins,
methyl cellulose, sodium carboxymethyl cellulose, and
other well-known suspending agents. Preferably, the
5   pharmaceutical preparation is in unit dosage form. In
such form, the preparation is subdivided into unit
doses containing appropriate quantities of the active
component. The unit dosage form can be a packaged
preparation, the package containing discrete quantities
10   of preparation, for example, packeted tablets,
capsules, and powders in vials or ampoules. The unit
dosage form can also be a capsule, cachet, or tablet
itself or it can be the appropriate number of any of
these in packaged form.

15   The quantity of active compound in a unit dose of
preparation may be varied or adjusted from 10 mg to
1000 mg according to the particular application and the
potency of the active ingredient.

         In therapeutic use as agents for treating
20   neurodegenerative diseases or disorders, the compounds
utilized in the pharmaceutical methods of this
invention are administered at the initial dosage of
about 1 mg/kg to about 30 mg/kg daily. A daily dose
range of about 3 mg/kg to about 10 mg/kg is preferred.
25   The dosages, however, may be varied depending upon the
requirements of the patient, the severity of the
condition being treated, and the compound being
employed. Determination of the proper dosage for the
particular situation is within the skill of the art.
30   Generally, treatment is initiated with smaller dosages
which are less than the optimum dose of the compound.
Thereafter, the dosage is increased by small increments
until the optimum effect under the circumstances is
reached. For convenience, the total daily dosage may
35   be divided and administered in portions during the day
if desired.

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The advantages of using the compounds of the instant invention include the relatively nontoxic nature of the compound, the ease of preparation, the fact that the compound is well tolerated, and the ease
5 of administration of the drug.

The following nonlimiting examples illustrate the preferred methods for preparing and using the compounds of the invention.

10   EXAMPLE 1

N-(2,6-Dichlorophenyl)-N'-4-pyridinyl urea

A solution of 4.7 g (0.05 mol) of 4-aminopyridine in 300 mL of anhydrous tetrahydrofuran was treated with 9.4 g (0.05 mol) of 2,6-dichlorophenylisocyanate. The
15 solution was heated at reflux for 24 hours, cooled, and concentrated in vacuo to a solid. Recrystallization from aqueous ethanol afforded the crystalline product, mp 217-219°C.

20   EXAMPLE 2

In a similar manner as described in Example 1, the following compounds were prepared by reacting the appropriate isocyanate with 3- or 4-aminopyridine:

N-(2,6-dichlorophenyl)-N'-3-pyridinyl urea,
25 mp 225-227°C;

N-(2,6-dimethylphenyl)-N'-3-pyridinyl urea,
mp 190-192°C;

N-(2,6-dimethylphenyl)-N'-4-pyridinyl urea,
mp 187-188°C;

30   N-(2,6-diethylphenyl)-N'-3-pyridinyl urea,
mp 196-197°C;

N-(2,6-diethylphenyl)-N'-4-pyridinyl urea,
mp 178-180°C;

N-(2-chloro-6-methylphenyl)-N'-3-pyridinyl urea,
35 mp 246-247°C; and

N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea,
mp 210-212°C.

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EXAMPLE 3

An in vitro model with rat hippocampal brain slices exposed to hypoxia-hypoglycemia was used to simulate ischemia. Neuroprotection was measured by the recovery of excitatory postsynaptic potentials after reoxygenation.

Oxygen tension was measured in superfusing solution and in slice tissue using polarized glass-insulated carbon fiber electrodes according to the methods of Jiang, et al (Brain Res 1991;568:159-64). The polarographic potential was -750 mV and the carbon fiber sensing element was 8 μm in diameter.

Young male Wistar rats (150 to 250 g) were anesthetized with ketamine (200 mg/kg IP) and ether and were perfused transcardially with cold, oxygenated, low sodium-containing physiological buffer solution (252 mM sucrose, 3.5 mM KCl, 1.0 mM $MgSO_4$, 20 mM $CaCl_2$, 26 mM $NaHCO_3$, 1.25 mM NaH_2PO_4, and 10 mM glucose) with 50 μM ketamine added. Brains were removed and hippocampi carefully excised. Hippocampi were sliced transversely at 450 μm and transferred into cold (4°C) low-sodium buffer solution gassed with 95% O_2, 5% CO_2 at 31°C. After 45 minutes slices were transferred to oxygenated normal physiological solution (126 mM NaCl, 3.5 mM KCl, 1.0 mM $MgSO_4$, 2.0 mM $CaCl_2$, 20 mM $NaHCO_3$, 1.25 mM NaH_2PO_4, and 10 mM glucose) at 31°C for at least 1 hour before experiments began. After preincubation, slices were transferred to a heated (36°C), gassed incubation chamber where they were continuously superfused with gassed normal physiological solution. Evoked extracellular synaptic potentials (EPSPs) were obtained using glass micropipettes placed approximately 100 μm into the slice. Electrical stimulation was applied once per minute to the stratum radiatum by insulated paired nichrome wires (60 μm diameter). Stimuli consisted of

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150 μA pulses lasting 0.4 msec. The 150 μA stimulus usually gave nearly a maximal EPSP (excitatory postsynaptic potential) amplitude. Data from a slice were used only if EPSP amplitude was greater than

5   2.0 mV before hypoxia-hypoglycemia.

Evoked potentials were recorded and analyzed with a digital computer interface. Experiments were started by recording for several minutes under normal conditions (95% O_2, 5% CO_2, 10 mM glucose). Then drug

10   was added to the superfusion solution (or normal solution was continued in control experiments). After 10 minutes of drug superfusion, hypoxia-hypoglycemia was induced by switching to superfusion solution containing added drug with low glucose (2 mM) that was

15   equilibrated with 95% N_2 and 5% CO_2. At the same time the slice chamber gas was switched to 95% N_2 and 5% CO_2. Hypoxia-hypoglycemia was continued for 12 minutes. After 12 minutes, 95% O_2 and 10 mM glucose were returned to the slices and the superfusing

20   solution. Following 15 minutes of reoxygenation, the experiment was ended. EPSPs were considered recovered if they returned to at least half of their original amplitude. The percentage of slices with recovered EPSPs were calculated for each condition.

25

Oxygen-Tension Measurements

Oxygen tension was measured in medium flowing through the experimental chamber. When the medium, as well as the gas within the chamber was switched from

30   95% oxygen to 95% nitrogen (carbon dioxide constant at 5%). Results in Figure 1A show that oxygen tension decreased from 95% to approximately 20% of saturation within 1 minute and then reached a plateau of approximately 5% after 4 minutes. Recovery of oxygen

35   tension in the medium upon reoxygenation was rapid, with complete recovery within 30 to 40 seconds.

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Oxygen tension was also measured approximately 100 μm deep within hippocampal slice tissue, a depth similar to that used for microelectrode voltage recordings. In stratum pyramidale, oxygen tension

5 under resting conditions was 50% to 65% of saturation as shown in Figure 1B. Oxygen tension in tissue is lower than in bathing medium, presumably because of oxygen utilization by the tissue in agreement with previous studies. After switching to hypoxic medium,

10 oxygen tension in tissue decreased more rapidly and completely than in superfusate, reaching less than 4% of saturation within 1 minute and falling to undetectable low levels within 2 minutes. Despite the rapid fall in oxygen tension, synaptic potentials and

15 population spikes in the CA1 cell body area were seen for at least 3.5 minutes after the start of hypoxia (a typical result in these experiments). Oxygenated medium was reapplied 9 minutes after the start of hypoxia. Oxygen tension in tissue returned to

20 approximately 75% of saturation over 4 to 5 minutes and then finally reached a resting level of approximately 55%. In this experiment as in many others without drug treatment, synaptic potentials never returned following more than 20 minutes of reoxygenation (see below). The

25 time course and extent of changes in tissue oxygen tension were similar in two other experiments with a shorter duration of hypoxia that allowed complete recovery of synaptic potentials (data not shown).

30 Synaptic Potential Measurement

Excitatory synaptic potential (EPSP) amplitude was measured before and during drug treatment in the 10-minute period preceding reduced oxygen and glucose. None of the drug treatments altered synaptic potentials

35 before hypoxia (data not shown). Without addition of drug (in control experiments), reduction of oxygen and

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glucose caused a rapid loss of synaptic potentials in each of 20 slices.

TABLE 1. Table Shows Effects of Different Concentrations of N-(2-chloro-6-methyl-phenyl)-N'-4-pyridinyl Urea on Recovery of Synaptic Activity (EPSP) in Hippocampal Slices After Hypoxia-hypoglycemia

Compound Tested	Concentration (μM)	Number Slices Recovered[b]/ Number Slices Tested	p-Value vs Control[a]
Controls	--	1/20	--
Test drug	0.5	0/8	NS
Test drug	2	3/8	0.058
Test drug	20	9/10*	<0.00001

* Significantly different than controls (p <0.05)
NS = Not significantly different than controls (p >0.1)
[a] p-Value by Fisher's exact test (two-tailed) compared to controls
[b] Slices with ≥50% EPSP amplitude recovery after reoxygenation

After 12 minutes of reduced oxygen and glucose and 15 minutes of recovery, EPSP amplitude was measured again. EPSP amplitude was scored as recovered if more than half of the initial value was recorded. Table 1 and Figure 2 show that treatment with N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea increased the percentage of slices that recovered EPSPs from approximately 5% (control) to 37% at 2 μM and 90% at a concentration of 20 μM (p <0.00001 by Fisher's exact test).

In Figure 2, drug concentrations are listed below each column. The 20 μM concentration of N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea gave almost complete protection from loss of EPSPs. [20 μM concentration—p <0.01 compared to control slices by

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Fisher's exact test (two-tailed); 2 μM
concentration—p <0.05].

In addition to increasing the number of slices
that reached a 50% criterion for recovery of EPSPs,
5   treatment with N-(2-chloro-6-methylphenyl)-N'-
4-pyridinyl urea significantly increased the mean EPSP
amplitude after hypoxia as a percentage of the control.
This was also a concentration-related effect that was
near significance at a concentration of 2 μM and was
10   significant with a high degree of confidence at 20 μM.

In Figure 3, use of N-(2-chloro-6-methylphenyl)-
N'-4-pyridinyl urea increased EPSP amplitude following
hypoxia in a concentration-dependent manner. Standard
error of the mean and p-values for significance
15   compared to controls for concentrations at 2 μM and
20 μM were as follows (Student's two-tailed t-test):
2 μM—p $\leq$0.07; 20 μM—p $\leq$0.0002. As indicated in the
graph, the use of 20 μM of N-(2-chloro-6-methylphenyl)-
N'-4-pyridinyl urea caused an almost complete recovery
20   of EPSPs.

Treatment with 0.5 μM of N-(2-chloro-6-methyl-
phenyl)-N'-4-pyridinyl urea resulted in changes from
hypoxia that were not different from control treatments
with no drug present.

25   Treatment with the two higher concentrations of
N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea
provides significant protection of hippocampal slices
from irreversible loss of synaptic potentials after
brief application of conditions that mimic ischemia
30   in vitro. Previous studies (Rock DM, McLean MJ,
Macdonald RL, et al, Epilepsy Res 1991;8:197-203) show
that N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea
modulates voltage-dependent sodium channels of nerve
cell membranes, and the inventors have determined that
35   this modulation provides protection from hypoxia. A
previous study with slices also shows that
tetrodotoxin, a very selective sodium channel blocker,

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delays negative shifts from hypoxia. Also, phenytoin,
another anticonvulsant, has shown effects preventing
neuronal damage from ischemia both in vitro and
in vivo. The results showed that treatment with
5   N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea
improves recovery of EPSPs at both 2 μM and 20 μM with
the 20 μM concentration giving almost complete
protection (9 out of 10 slices recovered).

N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea is
10   a modulator of neuronal voltage-gated sodium ion
channels. However, it is important to point out that
none of the concentrations tested reduced EPSP or
presynaptic action potential amplitude. Thus,
neuroprotection was obtained by modulating ion channels
15   without simply blocking them. These results suggest
that neuroprotection in vivo might be obtained at drug
doses that would not greatly alter normal neuronal
function.

Although the results with irreversible loss of
20   EPSPs do not directly demonstrate that the test drug
prevents ischemic neuronal cell loss, this hypothesis
can be tested using histological or biochemical
techniques. One hypothesis for the neuroprotective
action of this compound is that it blocks neuronal
25   hyperactivity or reduces sodium influx (by modulating
sodium channels) and therefore reduces energy demand
and preserves ion homeostasis, preventing
depolarization similar to that of spreading depression.
A similar hypothesis has been advanced for the
30   protection of white matter from hypoxic injury by local
anesthetic compounds. Also, a recent report suggests
that prevention of spreading depression-like events in
vivo underlie the action of certain drugs that prevent
tissue infarction from focal ischemia in rats (Gill,
35   et al, J Neuro 1992;67:236-40).

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In conclusion, this study provides evidence that the test drug or similar sodium ion channel modulating drugs prevent neuronal damage from ischemia.

EXAMPLE 4

5

This study was identical in design to Example 3 except that during the hypoxic period of 12 minutes, glucose was reduced from 10 mM to 2 mM rather than from 10 mM to zero as in Example 3.

10

Synaptic Potential Measurement

Without addition of drugs, hypoxia/hypoglycemia caused a rapid loss of synaptic potentials in each of 36 control slices. None of the drug treatments altered

15 synaptic potentials at the concentrations used (data not shown). However, lidocaine reversibly reduced both presynaptic action potential and EPSPs at a concentration of 500 μM (data not shown).

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TABLE 2.   Table Shows Effects of the Drugs Known to
           Interact With Voltage-dependent Sodium
           Channels on Recovery of Synaptic Activity
           (EPSP) in Hippocampal Slices After
           Hypoxia-hypoglycemia

Compound Tested	Concentration (μM)	Number Slices Recovered[a]/ Number Slices Tested	p-Value vs Control[b]
Controls	--	0/36	--
Phenytoin	5	0/8 (NS)	>0.1
Phenytoin	20	5/12*	0.0005
Phenytoin	50	3/9*	0.0059
Carbamazepine	20	2/9*	0.036
Carbamazepine	50	4/10*	0.0013
Lidocaine	50	5/9*	0.0001
Lidocaine	200	9/10*	<0.00001
Verapamil	1.0	3/8*	0.0042
Verapamil	10	5/9*	0.0001
Nimodipine	1.0	1/9 (NS)	>0.1

[a] Slices with ≥50% EPSP amplitude recovery after
    reoxygenation
[b] p-Value by Fisher's exact test (two-tailed)
    compared to controls
* Significantly different than controls (p <0.05)
NS = Not significantly different than controls
     (p >0.1)

Table 2 summarizes data obtained with drug
treatments.   Seven to 20 slices were recorded in each
drug condition and 36 control slices were studied
interspersed from time to time over the 4-month period
of experiments.

Drug treatment enhanced recovery of EPSPs
(especially with lidocaine, phenytoin, and verapamil).
Figure 4 shows the significance of EPSP recovery for
drug treatment in comparison to controls.

Standard error of the mean p-values for
significance compared to controls for the following
were found (students' two-tailed t-test):

20 μM phenytoin—p <0.01

50 μM phenytoin—p <0.01

50 μM carbamazepine—p <0.01

50 μM lidocaine—p <0.01

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200 μM lidocaine—p <0.01
20 μM carbamazepine—p <0.05

Drug intervention with four of the five drugs
during hypoxia-hypoglycemia provides significant
5   neuroprotection. All four drugs modulate sodium
channels. A previous study with slices also shows that
tetrodotoxin, a very selective sodium channel blocker,
delays loss of ion homeostasis from hypoxia. Results
with phenytoin are similar to those with other models
10   of ischemia in vitro and in vivo with models of focal
ischemia and global ischemia. Lidocaine treatment
improves recovery of EPSPs at both concentrations
tested, with 200 μM concentration giving almost
complete protection (9/10 slices recovered). Although
15   the use of lidocaine for ischemia in vivo is limited by
its peripheral hypotensive effects, one study reports
that brain damage from global ischemia in rabbits is
reduced by lidocaine and another recent study reports
neuroprotection by local anesthetics in a model of
20   white matter ischemia.

Each of the drugs in our study are modulators of
neuronal voltage-gated ion channels. However, it is
important to point out that none of the drugs reduced
EPSP or presynaptic action potential amplitude at the
25   concentrations used. Thus, neuroprotection was
obtained by modulating ion channels without simply
blocking them. These results suggest that
neuroprotection in vivo might be obtained at drug doses
that would not greatly alter normal neuronal function.

30   Several of these agents modulate calcium channels
as well as sodium channels. Phenytoin blocks a variety
of calcium channels at concentrations similar to those
tested here while carbamazepine and lidocaine are
thought to be more selective for sodium channels. In
35   addition to modulating sodium channels, verapamil is a
widely studied blocker of L-type calcium channels.
However, verapamil prevented ischemic damage at 10 μM

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but not at 1 μM. The 10 μM concentration is
supermaximal for blocking L-type channels but is near
the threshold for sodium channel. These results
suggest that the neuroprotective action of verapamil is
5   caused by action at sodium channels and not calcium
channels. This notion also is supported by results
with 1 μM nimodipine which failed to prevent loss of
EPSPs (nimodipine interacts with sodium channels at
concentrations greater than 10 μM). Tetrodotoxin, a
10 highly selective blocker of neuronal sodium channels,
previously has been reported to reduce neuronal damage
from global ischemia.

        Although the results with irreversible loss of
EPSPs do not directly demonstrate that sodium channel
15 modulators prevent ischemic neuronal cell loss, this
hypothesis can be tested using histological techniques.
One hypothesis for the neuroprotective action of these
compounds is that they block neuronal hyperactivity or
reduce sodium influx (by modulating sodium channels)
20 and therefore reduce energy demand and preserve ion
homeostasis.

        In conclusion, this study provides evidence that
these or similar ion channel modulating drugs prevent
neuronal damage from ischemia.

25

                        EXAMPLE 5
        An assay was conducted to compare the inhibitory
action of various compounds which are the subject of
the present invention. The assay measured the oxygen
30 deprivation-induced neuronal cell death from various
cortical cultures. The results of the assay are
provided in Table 3. Lactate dehydrogenase (LDH) is a
cytosolic enzyme that is only present in the
extracellular medium if cell membranes rupture,
35 indicating cell death. Therefore, LDH release into the
culture medium is a convenient assay of cell death.
The results of Table 3 indicate that each of the

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compounds tested decreased neuronal cell death from
hypoxia in vitro. These results suggest that each of
the compounds reduce damage from brain ischemia,
stroke, or neurodegenerative diseases.

5

Primary Culture Preparation

The uteri of Sprague Dawley rats in their 18th day
of fetal gestation were removed under halothane
anesthesia and placed in a chilled bath of magnesium
10   and calcium-free Hank's balanced salt solution (HBSS).
Cortical brain hemispheres were removed from individual
fetuses and digested in 0.1% trypsin in HBSS for
15 minutes at room temperature. Digested tissue was
washed three times with HBSS then dissociated into a
15   single cell suspension by trituration with a glass
pipette. Using a growth medium containing 42%
Delbecco's modified Eagle's medium with 42% HAM F12
nutrient supplement, 10% heat inactivated horse serum,
and 6% heat inactivated fetal calf serum (10/6
20   DME/F12), cell density was adjusted to one cortical
hemisphere per 10 mL of triturated suspension. One
hundred microliters of this cell suspension was
pipetted into individual wells of 96-well tissue
culture plates previously coated with poly-L-lysine,
25   then stored in a humidified incubator (37°C, 3% CO_2).
Glial cell growth was stopped by the addition of 100 μL
of 45% DME, 45% HAM F12, and 10% Horse serum
(10/0 DME/F12) containing 15 μg/mL of 5-fluoro-2-
deoxyuridine and 35 μg/mL of uridine, 3 days after the
30   initial plating. Cultures were fed at 2- or 3-day
intervals thereafter by replacing 100 μL of spent
medium with an identical volume of fresh 10/0 DME/F12.

Experimental Protocol

35   Sixteen-day-old cultures were prepared for
experiments by removing growth medium from each culture
well and rinsing once with 250 μL of Mg^{++}-free HBSS

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containing 1.8 mM Ca^{++} and 1 g/L D-glucose (0 Mg-HBSS).
Control and test agent solutions, prepared using
0 Mg-HBSS medium, were dispensed in 50 μL aliquots into
individual test wells (Total volume/well = 50 μL). All
5   liquid medium preparations to this point were
equilibrated with 95% oxygen, 5% CO_2. Plates were
placed into a 37°C, humidified, triple-gas incubator
with O_2 and CO_2 levels maintained at 1% and 10%,
respectively. Plates were removed after 7.5 hours of
10   oxygen deprivation and restored to normoxic conditions
(20% O_2/10% CO_2, 37°C) following a 50 μL addition to
each well of appropriate control or test agent
solutions containing 1.8 mM Ca^{++}, 1.6 mM Mg^{++}, and
7.0 g/L D-glucose. Final medium concentrations of
15   1.8 mM Ca^{++}, 0.8 mM Mg^{++}, and 4 g/L D-glucose were
present during the reoxygenation period.

Medium concentrations of lactate dehydrogenase
(LDH), a cytosolic enzyme normally retained by cells
but released upon cell death, were determined for each
20   well following an additional 16.5-hour normoxic
exposure period. Individual 25 μL medium specimens
were collected from each well and placed into wells of
a clean 96-well microtiter plate containing 225 μL of
0.1 M KPO_4 buffer (pH = 7.5 at 25°C) and 30 μg NADH
25   (reduced α-nicotinamide adenine dinucleotide). After
10-minute incubation at 37°C, 30 μL of 2.4 mM sodium
pyruvate was added to each well and plates were gently
shaken to mix solution. Plates were immediately placed
into a Multiscan MCC/340 plate reader and scanned for
30   fluorescence (excitation at 340 nM) for 1 minute at
5-second intervals. A kinetic analysis of the change
in medium absorbance resulting from shifts in NADH
concentrations was used, in combination with factors to
correct for temperature, light path, and volume
35   adjustments to determine medium LDH concentrations
(IU/mL). Normoxic control baseline LDH levels were
subtracted from both hypoxic control and test agent

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values prior to determining test agent effectiveness in preventing oxygen deprivation-induced injury.

5   TABLE 3.   Hypoxia-Induced Lactate Dehydrogenase Release (Cell Injury) in Neuronal/Glial Cortical Cultures

Test Group		LDH Release	% Inh[a]
Normoxic Control		74 ± 4	100%
Hypoxic Control		163 ± 11	0%
CPP	100 µM	80 ± 8	93%
TTX	3 µM	81 ± 5	92%
Lamotrigine	30 µM	102 ± 16	68%
	100 µM	89 ± 6	83%
Phenytoin	30 µM	93 ± 6	78%
	100 µM	90 ± 3	82%
N-(2,6-dichlorophenyl)-N'-4-pyridinyl urea	30 µM	107 ± 8	62%
	100 µM	84 ± 6	88%
N-(2,6-dimethylphenyl)-N'-4-pyridinyl urea	30 µM	68 ± 6	106%
	100 µM	91 ± 7	81%
N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea	30 µM	73 ± 6	101%
	100 µM	92 ± 4	80%
Carbamazepine	30 µM	116 ± 3	53%
	100 µM	78 ± 4	95%

LDH Release Determinations: n = 4 for each mean value.
[a] % Inh refers to the percent inhibition of the release of lactate dehydrogenase in comparison to hypoxic control cultures.

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CLAIMS

1. A method for treating neurodegenerative diseases
    or disorders which comprises administering a
    therapeutically effective amount of a compound
    having anticonvulsant properties which bind to
5   sodium channels and modulate the channel without
    blocking the channel, the compounds preventing
    irreversible neuronal damage from conditions
    similar to ischemia.

2. A method for treating neurodegenerative diseases
    or disorders as in Claim 1 which comprises
    administering a therapeutically effective amount
    of a compound of formula

wherein A is 4-pyridinyl; R_1 and R_2 are
independently halogen, lower alkyl, lower alkoxy,
or nitro, and R_3 is hydrogen, halogen, lower alkyl,
lower alkoxy, or nitro, or a pharmaceutically
acceptable acid addition salt thereof.

3. A method according to Claim 2 wherein the compound
    is administered in unit dosage form to a mammal in
    need of said treatment.

4. A method according to Claim 2 wherein the
    neurodegenerative disorder is acute brain injury.

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5.   A method according to Claim 2 wherein the
     neurodegenerative disorder is stroke.

6.   A method according to Claim 2 wherein the
     neurodegenerative disease is Alzheimer's disease.

7.   A method according to Claim 2 wherein the
     neurodegenerative disease is Huntington's disease.

8.   A method according to Claim 2 wherein the
     neurodegenerative disease is Amyotrophic Lateral
     Sclerosis.

9.   A method according to Claim 2 wherein the
     neurodegenerative disease is Parkinson's disease.

10. A method according to Claim 2 wherein the compound
     is N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea
     monohydrochloride or a pharmaceutically acceptable
     salt thereof.

11. A method according to Claim 2 wherein the compound
     is N-(2,3-dichlorophenyl)-N'-4-pyridinyl urea or a
     pharmaceutically acceptable salt thereof.

12. A method according to Claim 2 wherein an
     individual dose is administered in the range from
     about 10 mg to about 1000 mg intravenously of the
     compound or a pharmaceutically acceptable salt
5   thereof is administered.

13. A method according to Claim 3 wherein an
     individual dose is in the range from about 50 mg
     to about 2000 mg parenterally or about 50 to about
     5000 mg enterally of the compound or a
5   pharmaceutically acceptable salt thereof is
     administered.

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14. A method for treating neurodegenerative diseases
    or disorders as in Claim 1 which comprises
    administering a therapeutically effective amount
    of ralitoline.

15. A method for treating neurodegenerative diseases
    or disorders as in Claim 1 which comprises
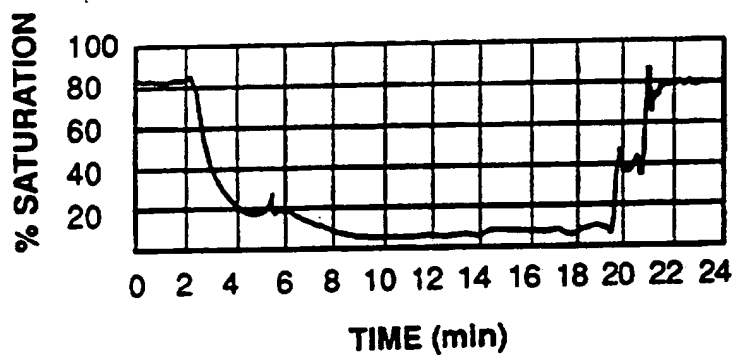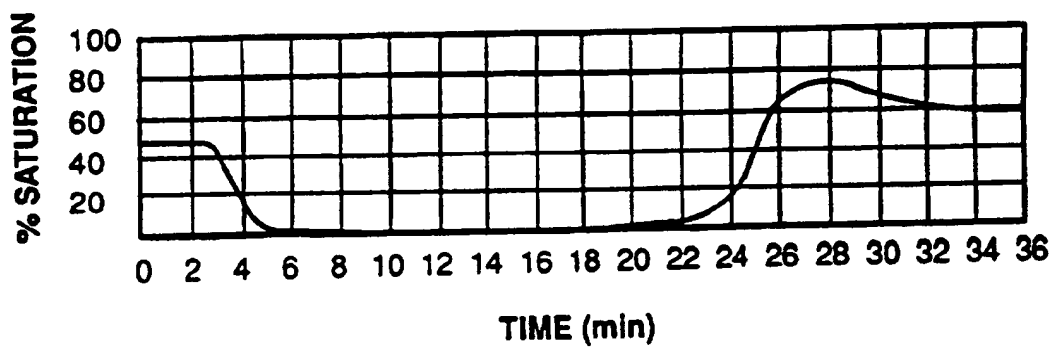   administering a therapeutically effective amount
    of phenytoin.

16. A method for treating neurodegenerative diseases
    or disorders as in Claim 1 which comprises
    administering a therapeutically effective amount
    of lamotrigine.

17. A method for treating neurodegenerative diseases
    or disorders as in Claim 1 which comprises
    administering a therapeutically effective amount
    of carbamazepine.

18. A method for treating neurodegenerative diseases
    or disorders as in Claim 1 which comprises
    administering a therapeutically effective amount
    of lidocaine.

19. A method for treating neurodegenerative diseases
    or disorders as in Claim 1 which comprises
    administering a therapeutically effective amount
    of tetrodotoxin.
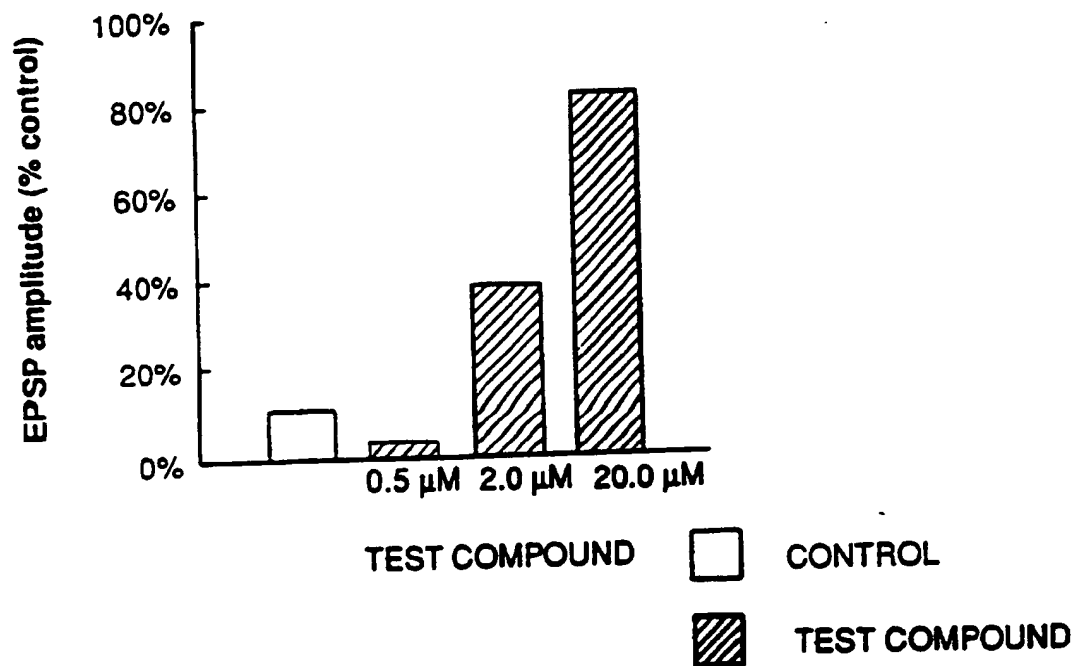
1 / 3

FIG. 1A

FIG. 1B

FIG. 2

FIG. 3

FIG. 4

CONTROL

PHENYTOIN(DPH)

CARBAMAZETINE(CBZ)

LIDOCAINE(LID)

VERAPAMIL(VER)

NIMODIPINE(NIM)

PCT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(72) Inventors: TAYLOR, Charles, Price, Jr.; 7560 Lake Shore Drive, Chelsea, MI 48118 (US). WEBER, Mark, Lawrence; 24678 Farmington Road, Farmington Hills, MI 48336 (US).

(74) Agents: ASHBROOK, Charles, W.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.

(81) Designated States: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, RU, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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(88) Date of publication of the international search report:
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(54) Title: METHODS FOR TREATING NEURODEGENERATIVE DISEASES AND DISORDERS USING N-(2,6-DISUBSTITUTED AROMATIC)-N'-PYRIDINYL UREAS AND OTHER ANTICONVULSANT COMPOUNDS

(57) Abstract

The instant invention is novel uses of known N-(2,6-disubstituted phenyl)-N'-3- and 4-pyridinyl ureas and pharmaceutically acceptable acid addition salts thereof. Such compounds as N-(2-chloro-6-methylphenyl)-N'-4-pyridinyl urea monohydrochloride or N-(2,3-dichlorophenyl)-N'-4-pyridinyl urea are used for treating neurodegenerative disorders, perinatal asphyxia, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. The instant invention is similar novel uses of known anticonvulsant compounds as ralitoline, phenytoin, lamotrigine, tetrodotoxin, lidocaine, and carbamazepine.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5   A61K31/44   A61K31/415   A61K31/53   A61K31/55   A61K31/165
        A61K31/425   A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5   A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 135 335 (WARNER-LAMBERT COMPANY) 27 March 1985 see claims 1-10 & US,A,4 629 731 (IDEM) cited in the application ---	1-13
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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 1994	1 0. 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl. Fax (+ 31-70) 340-3016	Theuns, H

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT	
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X	CAN.J.ANAESTH., vol.37, no.7, October 1990 pages 762 - 777 R.HALL ET AL. 'Brain protection: physiological and pharmacological considerations. Part II: The pharmacology of brain protection' see page 767 see page 771 ---	1-13,15
X	METHODS FIND. EXP. CLIN. PHARMACOL., vol.12, no.1, 1990 pages 17 - 22 S.N.THOKAT ET AL. 'The Protective Effect of Adenosinergic Agents, Ro 5-4864 and Carbamazepine against Hypoxic Stress-Induced Neurotoxicity in Mice' see abstract ---	1-13
X	STROKE, vol.21, no.11SU, November 1990 pages III-47 - III-51 P.A.BOXER ET AL. 'Comparison of Phenytoin With Noncompetitive N-Methyl-D-Aspartate Antagonists in a Model of Focal Brain Ischemia in Rat' * see abstract, last sentence * --- -/--	1-13,15

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	DIALOG INFORMATION SERVICES, FILE 5: BIOSIS PREVIEWS, ACCESSION NUMBER 10861114 see abstract & SOC. NEUROSCI.ABSTR., vol.19, no.1-3, 1993 page 1657 M.G.VARTANIAN ET AL. 'Phenytoin and CI 953 attenuate hypoxic-ischemic brain damage in neonatal rats' ---	1-13
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X	REV.MéD.LIèGE, vol.34, no.20, 15 October 1979 pages 839 - 845 M.CORDONNIER ET AL. 'FASCICULATIONS MALIGNES ET BÉNIGNES. A PROPOS D'UN CAS DE NEUROMYOTONIE' see page 843 --- -/--	1,15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	J.PHARMACOL.EXP.THER., vol.266, no.3, September 1993 pages 1549 - 1555 R.FERN ET AL. 'Pharmacological Protection of CNS White Matter during Anoxia: Actions of Phenytoin, Carbamazepine and Diazepam' see abstract ---	1,15
X	BRAIN RES., vol.558, no.1, 1991 pages 127 - 130 P.E.POTTER ET AL. 'Diphenylhydantoin attenuates hypoxia-induced release of [3H]glutamate from rat hippocampal slices' see the whole document ---	1,15
X	EUR.J.PHARMACOL., vol.128, no.3, 9 September 1986 pages 255 - 257 E.MELAMED ET AL. 'Diphenylhydantoin and phenobarbital suppress the dopaminergic neurotoxicity of MPTP in mice' see abstract ---	1,15
X	J.NEUROSURG., vol.60, no.3, March 1984 pages 467 - 472 L.J.WILLMORE ET AL. 'Effect of phenytoin and corticosteroids on seizures and lipid peroxidation in experimental posttraumatic epilepsy' see abstract ---	1,15
X	EP,A,0 427 925 (WARNER-LAMBERT COMPANY) 22 May 1991 see page 2, line 52 - page 3, line 18 ---	1,15
X	J.CEREB.BLOOD FLOW METAB., vol.2, no.SUP1, 1982 pages S59 - S61 E.M.NEMOTO ET AL. 'Free Fatty Acids (FFA) in the Pathogenesis and Therapy of Ischemic Brain Injury' see page S59, last paragraph ---	1,15
X	PRESSE MéD., vol.20, no.18, 11 May 1991 pages 841 - 845 J.C.PECHADRE ET AL. 'Prévention de l'épilepsie post-traumatique tardive par phénytoïne dans les traumatismes crâniens graves. Suivi durant 2 ans' see abstract ---	1,15

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BR.J.HOSP.MED., vol.35, no.5, May 1986 pages 290 - 298 A.AITKENHEAD ET AL. 'Cerebral protection' see page 295 ---	1,15
X	CHEMICAL ABSTRACTS, vol. 91, no. 13, 24 September 1979, Columbus, Ohio, US; abstract no. 102275q, see abstract & D.GUASTAMACHIO 'The effect of diphenylhydantoin and procainamide on aluminium-induced Alzheimer-type neurofibrillary tangles in rabbit brain' 1979 -----	1,15

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

For further information please see annex

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see annex.

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

claim 1 partially, claims 2-13
and claim 15.

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

FURTHER INFORMATION CONTINUED FROM   PCT/ISA/210

Continuation of BOX I.2:

Claims searchable completely: 2-19
Claims searchable incompletely: 1

The definition of compounds by means of their pharmacological profile instead of structural parameters makes a complete search for the subject matter of claim 1 virtually impossible.

Although all claims are directed to a method of treatment of the human/animal body the search has been based on the alleged effects of the compounds.

Continuation of BOX II:

1. Use of compounds of formula 1 for the manufacture of medicaments for treating neurodegenerative diseases (claim 1 partially, and claims 2-13).
2. Use of ralitoline for the manufacture of medicaments for treating neurodegenerative diseases (claim 1 partially, and claim 14).
3. Use of phenytoin for the manufacture of medicaments for treating neurodegenerative diseases (claim 1 partially, and claim 15).
4. Use of lamotrigine for the manufacture of medicaments for treating neurodegenerative diseases (claim 1 partially, and claim 16).
5. Use of carbamazepine for the manufacture of medicaments for treating neurodegenerative diseases (claim 1 partially, and claim 17).
6. Use of lidocaine for the manufacture of medicaments for treating neurodegenerative diseases (claim 1 partially, and claim 18).
7. Use of tetrodotoxin for the manufacture of medicaments for treating neurodegenerative diseases (claim 1 partially, and claim 19).

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	3142684	28-02-85
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		JP-B-	6025113	06-04-94
		JP-A-	60058962	05-04-85
		US-A-	4629731	16-12-86
		US-A-	4962116	09-10-90
US-A-4629731	16-12-86	US-A-	4962116	09-10-90
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		AU-A-	3142684	28-02-85
		CA-A-	1246084	06-12-88
		EP-A,B	0135335	27-03-85
		JP-B-	6025113	06-04-94
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